REVIEW

Sympathetic Neural Mechanisms in Human Cardiovascular Health and Disease

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The sympathetic nervous system plays a key role in regulating arterial blood pressure in humans. This review provides an overview of sympathetic neural control of the circulation and discusses the changes that occur in various disease states, including hypertension, heart failure, and obstructive sleep apnea. It focuses on measurements of sympathetic neural activity (SNA) obtained by microneurography, a technique that allows direct assessment of the electrical activity of sympathetic nerves in conscious human beings. Sympathetic neural activity is tightly linked to blood pressure via the baroreflex for each individual person. However, SNA can vary greatly among individuals and that variability is not related to resting blood pressure; that is, the blood pressure of a person with high SNA can be similar to that of a person with much lower SNA. In healthy normotensive persons, this finding appears to be related to a set of factors that balance the variability in SNA, including cardiac output and vascular adrenergic responsiveness. Measurements of SNA are very reproducible in a given person over a period of several months to a few years, but SNA increases progressively with healthy aging. Cardiovascular disease can be associated with substantial increases in SNA, as seen for example in patients with hypertension, obstructive sleep apnea, or heart failure. Obesity is also associated with an increase in SNA, but the increase in SNA among patients with obstructive sleep apnea appears to be independent of obesity per se. For several disease states, successful treatment is associated with both a decrease in sympathoexcitation and an improvement in prognosis. This finding points to an important link between altered sympathetic neural mechanisms and the fundamental processes of cardiovascular disease.

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MI = myocardial infarction; MSNA = muscle sympathetic neural activity; OSA = obstructive sleep apnea; SA = sinoatrial; SNA = sympathetic neural activity

The sympathetic nervous system plays a vital role in the everyday lives of human beings. Sympathetic neural responses are essential to simple tasks such as changing posture. Movement from a supine or sitting position to an upright position requires complex adjustments in blood flow and blood pressure, and these adjustments are ultimately coordinated by sympathetic nerves in conjunction with parasympathetic modulation of heart rate. Without such adjustments, blood flow to the brain would fall below autoregulatory limits, and standing up would consistently cause syncope. Indeed, some persons with severe autonomic failure are unable to stand (or sometimes even to sit upright) without fainting.[1,2]

This article presents an overview of our current understanding of sympathetic neural mechanisms in human cardiovascular control. It focuses on measurements of sympathetic neural activity (SNA) that are obtained by microneurography, a technique that can directly measure the electrical activity of sympathetic nerves in intact, conscious human beings. During the past 3 decades, the information yielded by this technique has greatly increased our clinical and mechanistic understanding of sympathetic neural mechanisms in health and disease. Ongoing research using this technique continues to yield new insights into the pathophysiology of cardiovascular diseases, including hypertension, coronary artery disease, and heart failure, and into the cardiovascular risk associated with diseases such as obstructive sleep apnea (OSA) and obesity.

SYMPATHETIC NEURAL MECHANISMS IN THE REGULATION OF BLOOD PRESSURE

Sympathetic neural influences on cardiovascular function can be divided into 4 main categories: the influences of cardiac sympathetic nerves, the influences of vascular sympathetic nerves, adrenal medullary influences caused by circulating epinephrine and norepinephrine, and the sympathetic stimulation of renal juxtaglomerular cells that activates the renin-angiotensin-aldosterone axis. Most sympathetic innervation in the human cardiovascular system is noradrenergic. Norepinephrine is the primary neurotransmitter, and epinephrine and other cotransmitters perform secondary functions (with the exception of sympathetic sudomotor innervation, which is cholinergic, and the action of sympathetic active vasodilator nerves in human skin, which results from cholinergic cotransmission[3]).

Cardiac sympathetic innervation of the heart includes innervation of the sinoatrial (SA) node, which allows sympathetic nerves to increase heart rate by increasing the slope of diastolic depolarization during the spontaneous SA node action potential. Sympathetic nerves also innervate the myocardium; increases in sympathetic activity increase myocardial contractility and, therefore, increase stroke volume. Sympathetic innervation of the peripheral vasculature causes vasoconstriction primarily through the action of norepinephrine at postsynaptic α-adrenergic re-

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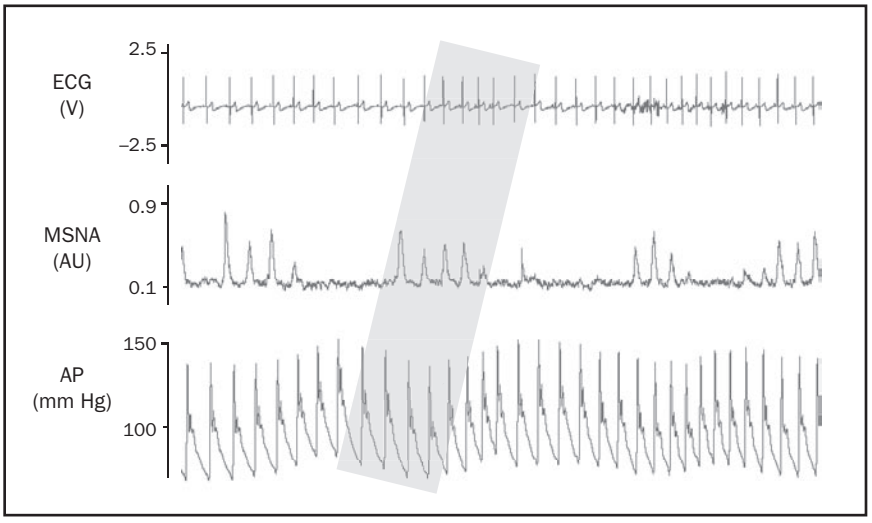

FIGURE 1. Electrocardiogram (ECG), integrated sympathetic neurogram, and plot of beat-to-beat arterial pressure (AP) (as measured by a brachial artery catheter) from a healthy person. The figure shows the dynamic relationship between AP and muscle sympathetic neural activity (MSNA). The shading highlights an example of a transient decrease in AP that elicits an increase in MSNA via the baroreflex. This increase causes vasoconstriction, which in turn increases AP and leads to a reflex decrease in MSNA.

ceptors. Cotransmitters such as neuropeptide Y also have a role in this vasoconstriction.[4,5]

Short-term Blood Pressure Responses

The primary recognized role of the sympathetic nervous system in cardiovascular control is the maintenance of blood pressure and the regulation of blood flow for seconds to minutes via the arterial baroreflex. However, this view of the sympathetic nervous system is evolving as new evidence emerges about its additional role in the long-term regulation of blood pressure.[6-9]

The arterial baroreflex senses changes in blood pressure via baroreceptors, which are sensory afferent nerve endings located in the carotid sinus and the aortic arch. The baroreceptors respond to stretching of the vessel wall. In general, increases in this stretching as the result of a short-term increase in blood pressure lead to an increase in afferent input into central autonomic nuclei (notably the nucleus tractus solitarius). This increase in afferent input results in a reflex decrease in sympathetic neural outflow, which in turn decreases vasoconstrictor tone, myocardial contractility (to decrease stroke volume), and heart rate. All of these influences then result in a correction of the original "error signal" of increased blood pressure. These sympathetic influences work in conjunction with parasympathetic influences on the SA node to decrease heart rate. During a short-term decrease in blood pressure, the opposite occurs, and the autonomic nervous system acts to increase vasoconstriction, increase stroke volume, and increase heart rate.

The arterial baroreflex also responds to the normal small variations in blood pressure that are continually induced by the respiratory cycle and by changes in posture in healthy, resting humans. Figure 1 shows an electrocardiogram, a neurogram of SNA (measured by microneurography), and a plot of beat-to-beat blood pressure data from a healthy person. Each upward deflection in the neurogram represents a "burst" of SNA, which is a collection of action potentials in sympathetic vasoconstrictor nerves, in this case those innervating the lower leg and foot. The shading highlights a small decrease in blood pressure over the course of a few heartbeats, which elicits an increase in sympathetic vasoconstrictor nerve activity (and increased heart rate) via the baroreflex. These baroreflex responses result in a small increase in pressure, which then inhibits nerve activity, also via the baroreflex. This repeating pattern results in a strong inverse relationship between blood pressure and SNA, even under resting conditions.

Somewhat less well understood are cardiopulmonary baroreceptors. These receptors are located in the walls of the atria and the ventricles, and they appear to respond more to changes in volume than to changes in pressure. Ultimately, they work in concert with the arterial baroreceptors to buffer changes in blood pressure so that swings in pressure are not overly dramatic and therefore do not harm the organism.

Direct measurement of SNA in muscle vasculature has revealed that sympathetic nerve traffic varies in response to the amount of pressure generated by each beat of the heart. The sympathetic nervous system responds even within a

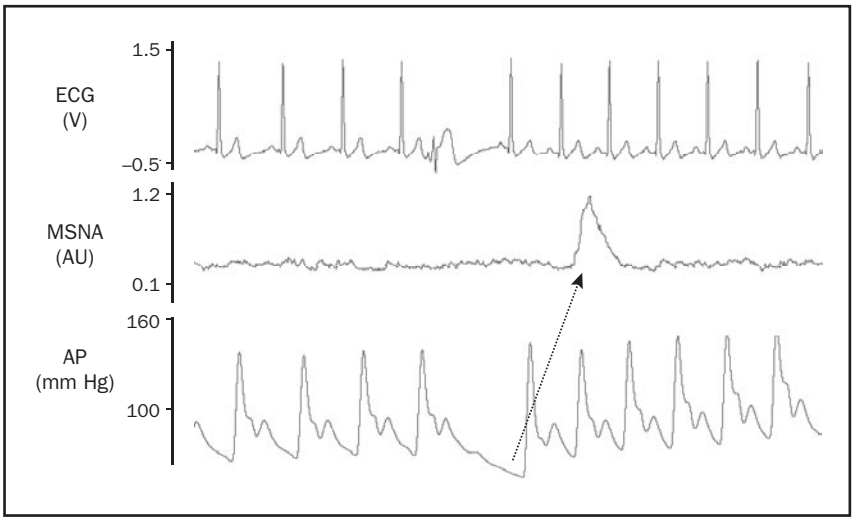

FIGURE 2. Electrocardiogram (ECG), integrated sympathetic neurogram, and plot of beat-to-beat arterial pressure (AP) from a healthy person. The ECG tracing shows a premature ventricular contraction that is associated with an ineffective beat. The subsequent decrease in diastolic pressure elicits a large reflex burst of muscle sympathetic neural activity (MSNA). The arrow indicates the relationship between the low diastolic pressure and the elicited burst of MSNA.

single cardiac cycle to the momentary drop in blood pressure induced by an extrasystole. Figure 2 shows SNA, along with an electrocardiogram and a plot of beat-to-beat arterial pressure, on a more expanded timescale than that shown in Figure 1. As illustrated, a premature ventricular contraction leads to excessive reduction of diastolic pressure for 1 cardiac cycle. Even this momentary alteration in blood pressure elicits an immediate and dramatic increase in SNA.

Respiration induces physiologic swings in stroke volume and blood pressure because of changes in both preload and afterload of the right and left ventricles. These changes, which are caused by fluctuations in intrathoracic pressure, can also be sensed by, and can elicit responses in, arterial and cardiopulmonary receptors. Changes in posture also induce changes in blood pressure because of changes in preload, and the baroreflex responds to correct the blood pressure, thereby preserving cerebral perfusion and the ability to maintain the upright position. For example, when a human being stands, a decrease in venous return can lead to a decrease in pulse pressure, systolic pressure, and/or diastolic pressure. This decrease in pressure decreases the rate of firing by baroreceptors in the aortic arch and the carotid sinus, and this change leads to a baroreflex-mediated increase in sympathetic neural outflow to the heart and the peripheral vasculature. This change in neural outflow increases vascular tone, stroke volume, and heart rate so that the level of arterial pressure can be maintained or corrected.

The sensitivity of the baroreflex is defined as the amount of change in SNA for a given change in blood pressure and can be viewed as the responsiveness of the reflex to challenges to blood pressure. This sensitivity varies over time and from person to person. When the sympathetic baroreflex is less sensitive, the response of the sympathetic nerves to a given change in arterial pressure will be less pronounced and may be less able to return the pressure to baseline levels.

Long-term Regulation of Blood Pressure

In contrast to the traditional view that the sympathetic nervous system is responsible only for the short-term regulation of blood pressure, the results of recent studies suggest that sympathetic neural mechanisms play important roles in the long-term regulation of blood pressure.[6-9] Importantly, dysfunction in these pathways may be responsible for the pathophysiology of some forms of "idiopathic" hypertension.

The long-term role of sympathetic nerves in blood pressure regulation was previously discounted in part because the baroreflex can "reset" the level around which it regulates blood pressure. If the reflex resets itself over time to the prevailing blood pressure level, then it can be of little use in correcting long-term elevated blood pressure. However, the results of recent work by Lohmeier et al[10] indicate that the baroreflex may be able to correct blood pressure, and to sense an error signal, without resetting, for periods of several days to weeks. Their study found that long-term stimulation of afferent nerves in the baroreflex arc de-

creased arterial pressure, presumably by inhibiting efferent sympathetic neural activity for a week or longer.

Osborn et al[7,8] have proposed the concept of a central nervous system "setpoint" that is separate from the baroreflex and involves central autonomic mechanisms. These are central neural mechanisms that set the long-term level of blood pressure by providing input to sympathetic premotor neurons in the rostral ventrolateral medulla via mechanisms independent of baroreceptor afferent input. These central nervous system areas appear to receive input from volume-regulatory hormones such as angiotensin II, perhaps explaining the importance of this and related hormones in animal models of hypertension, which also depend on the sympathetic nervous system.[7,11] In addition to these findings from animal models, the results of our recent studies of interindividual variability in the action of sympathetic neural mechanisms in regulating blood pressure provide some initial evidence that the sympathetic nervous system plays an important role in long-term blood pressure control in humans.[12,13] These findings may have implications for the treatment of chronic cardiovascular disease.

MEASURING SNA IN HUMANS

Direct Measurement

Because sympathetic postganglionic neurons are small, unmyelinated C fibers, it was originally thought that their activity could not be directly measured in humans. In the late 1960s, a group of Swedish investigators pioneered the method of microneurography for measurement of human neural activity and somewhat accidentally came upon the sympathetic vasoconstrictor nerve signal.[14] Since the 1970s, microneurography has been used successfully to elucidate the complex integrative physiology related to neural control of the circulation in intact humans.[15,16]

In humans, SNA is most often measured at the peroneal nerve, and the most common measurement is muscle sympathetic neural activity (MSNA). The technique involves the percutaneous insertion of a high-impedance tungsten microelectrode (the tip of which is only a few microns in diameter). Fine adjustments are made with the electrode until a suitable signal is achieved. Most sympathetic neural recordings involve "multiunit" recordings, which simultaneously record signals from several individual neurons. Single-neuron recordings are also possible but are more technically demanding, both for recording and for analyzing the signal.[17-19]

One of the defining characteristics of SNA in humans is that the sympathetic nerves exhibit spontaneous "bursts" of activity. These bursts represent the coordinated activity of several individual nerve fibers. The MSNA signal is made up entirely of sympathetic vasoconstrictor nerves and is strongly regulated by the arterial baroreflex. As shown in Figure 1, decreases in blood pressure elicit reflex increases in MSNA, which cause vasoconstriction, thereby increasing blood pressure and causing reflex decreases in MSNA. This cycle continues and can be observed in most healthy persons, even when supine, as normal variations in blood pressure. Additionally, as already noted, sympathetic neurally mediated vasoconstriction is a key response in the arterial baroreflex and is essential for successful assumption of the upright posture.[20,21] In contrast, skin SNA, for example, which also involves sudomotor, vasodilator, and pilomotor fibers, is not strongly regulated by the baroreflex.

Norepinephrine Spillover Technique: Measurement of Nonmuscle SNA

The kinetics of norepinephrine metabolism involve a complex series of steps, including the release, reuptake, and metabolism of norepinephrine. A certain percentage of the norepinephrine released from sympathetic nerve endings "spills over" into the circulation and contributes to the concentration of norepinephrine in circulating plasma, although changes in other aspects of norepinephrine kinetics also contribute to this concentration. Thus, an increase in plasma concentrations of norepinephrine could be the result of an increase in the release of norepinephrine, but it could also be a result of the decrease in reuptake, a decrease in metabolism, or some combination of changes in all 3 of these variables.

In the mid-1980s, Esler et al[22] developed a technique for measuring SNA by using isotope-dilution principles to measure the spillover of norepinephrine from specific regional circulations. This norepinephrine spillover technique, which involves the infusion of tritiated norepinephrine and regional sampling of blood from the coronary sinus (for cardiac norepinephrine spillover) or the renal vein (for renal norepinephrine spillover), provides information about the activity of sympathetic nerves in regions that are not accessible by percutaneous microneurography, such as the heart and kidney. It allows regional sympathetic activity to be directly measured in intact persons. However, the approach is quite complex and invasive and may not be feasible in many scenarios. In this context, it is of interest (as already noted) that MSNA in young men (as measured by microneurography) is positively correlated with norepinephrine spillover to the heart and kidney and with whole-body norepinephrine spillover.[23,24]

INTERINDIVIDUAL VARIABILITY: ROLE IN REGULATION OF BLOOD PRESSURE

Two characteristics of MSNA have perplexed both clinicians and scientists for several decades. The first is the striking interindividual variability in the amount of neural

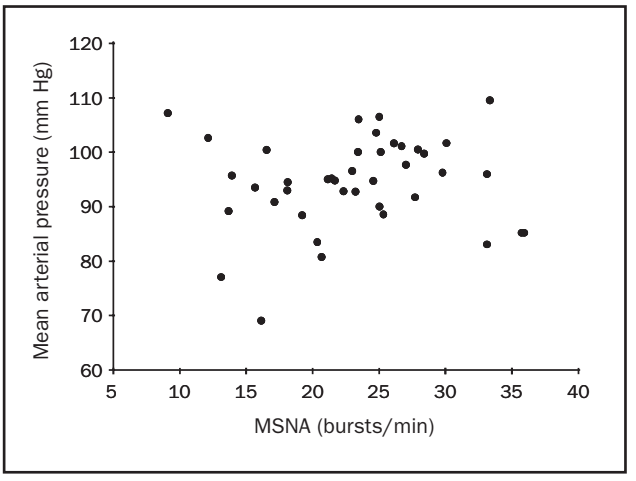

FIGURE 3. Resting values for muscle sympathetic neural activity (MSNA) and mean arterial pressure in 41 healthy men. The figure shows the absence of an association between these variables. Although MSNA values range widely among healthy persons, the arterial pressure levels are not consistently higher among persons with very high MSNA than among those with much lower MSNA.

activity in resting humans. Muscle sympathetic neural activity can exhibit a 7- to 10-fold variation in healthy humans, a fact that was initially disappointing to investigators who thought that a narrower range of "normal values" would allow the use of MSNA measurements for clinical diagnostic purposes. However, the more recent results of studies performed in our laboratory suggest that this interindividual variability may provide key information about integrative mechanisms of long-term blood pressure regulation. The second is that, despite the tight relationship between MSNA and blood pressure (via the baroreflex) for a given person, MSNA can vary greatly among individuals and that variability does not appear to be related to blood pressure. For example, a person with very low MSNA may have the same arterial pressure as a person with very high MSNA. This finding initially seemed counterintuitive in light of the strong relationship among MSNA, vasoconstriction, and blood pressure (ie, if an increase in SNA increases blood pressure in a given person, how is it possible that the blood pressure of a person with long-term elevated SNA may be lower than that of a person whose SNA is not elevated?). This striking interindividual variability and the absence of an association between SNA and blood pressure are shown in Figure 3, which presents data collected in our laboratory from 41 normotensive men during the past 5 years.

In an era when the importance of "individualized medicine" is receiving increasing attention, we have become interested in the differences among individuals in factors that help maintain normal blood pressure. Rather than taking averages of data from large groups, we have been viewing interindividual differences as important in and of themselves. In this context, we have recently conducted several studies to examine hemodynamic factors that may balance the vasoconstrictor (and pressor) influences of various levels of SNA. The results of our studies of the interindividual variability in MSNA have helped us gain insight into the integrative physiological mechanisms used by the human body to balance various levels of activity by sympathetic vasoconstrictor nerves. For example, young men with high MSNA (and high peripheral vascular resistance) have lower cardiac output, which appears to "balance" the higher vascular resistance (arterial pressure is the product of cardiac output and total peripheral resistance).[12] Other factors, such as variability in the responsiveness of blood vessels to adrenergic stimulation, also appear to contribute to this integrated balance.[13] In a recent study, we found striking differences between men and women in the relationships among blood pressure, vascular resistance, and cardiac output.[25] More work is needed in this area so that we can determine which shifts or dysregulation in these balances are likely to accompany specific diseases such as hypertension.

Other factors associated with MSNA are also important to the foregoing discussion. First, although MSNA can be quite variable from person to person, the signal is very reproducible in a given person.[26,27] Thus, MSNA measurements obtained on one occasion will be very similar to those obtained from the same person months to a year or more later. (Because MSNA increases with age, however, a period of several years between measurements will be associated with a small increase in MSNA.) Second, in healthy young men, MSNA appears to be representative of SNA in other vascular beds in the human body; examples are cardiac and renal SNA as measured by norepinephrine spillover.[23,24] In young men, MSNA is also strongly positively correlated with whole-body norepinephrine spillover[24] and with total peripheral resistance[12]; these findings suggest that MSNA is a good index of whole-body "net" sympathetic vasoconstrictor tone in healthy young men.

LONG-TERM MODIFIERS OF SYMPATHETIC ACTIVITY

Physiology

Aging. Even in the absence of disease, MSNA increases with age, on average by approximately 1 burst per minute each year.[26] This age-related increase in sympathetic activity may contribute to the increase in the risk of hypertension with aging. Indeed, in persons older than 40 years, a strong association exists between resting levels of MSNA and resting arterial blood pressure.[28] This association does not exist in younger persons, suggesting that mechanisms

TABLE. **Conditions Associated With Increases in Resting MSNA and Interventions That Decrease It in Patients With These Conditions**

Condition or pathophysiology	Intervention
Essential hypertension	Chronic β-blockade (≥3 wk)
Obesity	Weight loss, particularly decrease in waist circumference
Heart failure	Exercise training; heart transplant
Unstable angina or acute myocardial infarction	None. MSNA decreases over time after resolution of acute event
Obstructive sleep apnea	Treatment with continuous positive airway pressure
Dehydration	Rehydration, oral or intravenous

MSNA = muscle sympathetic neural activity.

that buffer or balance the hypertensive influences of higher MSNA are less active or missing in older persons.[12,29] Interestingly, the increase in sympathetic activity with age is more marked in women than in men, as is the increase in the risk of cardiovascular disease.[28] Resting levels of MSNA are on average lower in women than in men,[25] but this difference in MSNA levels between men and women becomes minimal around the age of menopause, and resting MSNA levels in women older than 60 years have been shown to be even higher than those in their male counterparts.[28]

Sex. Overall, young women exhibit lower MSNA levels, lower blood pressure, and lower cardiac output than young men.[25,30] As already noted, this difference changes with age; after menopause, women can exhibit MSNA levels that are similar to or even higher than those of men of a similar age.[28]

It has become clear that female sex steroids alter SNA, although the specific mechanisms by which they do so remain to be determined. Women exhibit variations in MSNA that are associated with fluctuations of the female sex hormones during the phases of the menstrual cycle. For example, the preovulatory estrogen surge is associated with an increase in MSNA responses.[31] Additionally, MSNA is higher during the midluteal phase of the menstrual cycle, when both estrogen and progesterone levels are increased, than it is during the early follicular phase of the cycle, when the levels of both hormones are low.[32] Sympathetic activation also occurs during the early and late stages of pregnancy.[33] For research purposes, MSNA measurements in women are often made during the early follicular phase or the placebo phase of oral contraceptive use so that any influences of female reproductive hormones on sympathetic mechanisms can be minimized.

With regard to interindividual variability in blood pressure regulation, we recently reported striking differences between the sexes in the associations between SNA and central hemodynamics.[25] In healthy young persons of either sex, SNA and blood pressure levels do not correlate. In young men, the level of resting MSNA is balanced by vascular responsiveness and cardiac output (ie, in a healthy young man with high MSNA, normotension is maintained by lower levels of cardiac output and less vascular responsiveness to norepinephrine). However, in women no correlation exists between MSNA and either cardiac output levels or total peripheral resistance.[25] Because women also exhibit substantial interindividual variability in MSNA, this surprising finding implies that women and men must differ in the mechanisms by which high sympathetic activity is balanced so as to maintain normotension. One potential difference is the influence of estrogen in promoting vasodilation via nitric oxide or β-receptors; this influence may underlie the disconnect between MSNA and total peripheral resistance in women.[25]

Pathophysiology

A number of conditions have been associated with elevations in MSNA, including hypertension, obesity, heart failure, coronary artery disease, OSA, and dehydration (Table).

Essential Hypertension

Persons with essential hypertension exhibit elevations in MSNA, and MSNA increases progressively with the degree of hypertension.[34-37] This is true for patients of all ages[34] and those with low borderline, high borderline, or overt hypertension,[38] but the elevations are not as marked among women with hypertension as among men with hypertension.[39] Sympathetic activation among patients with hypertension may be associated with an increase in cardiovascular risk and an increase in end-organ damage.[40] In this context, long-term antihypertensive treatment with β-blockers has been shown to decrease resting MSNA.[41,42] Although this effect is due in part to the influence of β-blockers in decreasing resting heart rate (ie, each cardiac cycle can produce 1 burst of sympathetic activity), the net effect is less sympathetic activity per minute.[41,42] The decrease in MSNA may contribute to the antihypertensive effects of β-blockade. In contrast, long-term treatment with angiotensin II receptor blockers such as losartan has been shown to have no effect on[43] or to increase[44] MSNA, even though it effectively reduces blood pressure.

The causes of sympathoexcitation in association with idiopathic hypertension are unclear but may involve increases in chemoreflex sensitivity to hypoxia or hypercapnia:

the responses to chemoreflex stimulation among hypertensive patients are several times higher than the responses exhibited by normotensive controls.[45,46] Interestingly, secondary hypertension does not appear to be associated with increased MSNA.[37]

Obesity

Muscle sympathetic neural activity is increased markedly among obese patients and decreases with weight loss induced by exercise and diet.[47,48] It is positively correlated with the amount of abdominal visceral fat, the amount of total abdominal fat, the waist-to-hip ratio, the percentage of body fat, the waist circumference, and the body mass index.[49] Overall, evidence suggests that elevated MSNA may contribute to hypertension and cardiovascular disease among obese patients.[50] Muscle sympathetic neural activity is most closely correlated with the amount of abdominal visceral fat as measured by computed tomography; this relationship is independent of total body fat.[49] This correlation may be a mechanistic link in the association between cardiovascular disease and visceral obesity.

Heart Failure

Among patients with heart failure, MSNA is strikingly increased.[51,52] In terms of the occurrence of sympathetic bursts, a healthy person may experience 30 to 50 bursts per 100 heartbeats, whereas patients with heart failure can experience as many as 90 to 100 bursts per 100 heartbeats (ie, 1 burst in every cardiac cycle). This extreme sympathoexcitation has been shown to be a predictor of mortality for patients with heart failure.[53] Interestingly, a longitudinal study involving patients with ischemic cardiomyopathy who underwent heart transplant and were followed up 1 year after the procedure showed that MSNA decreases rapidly during the month after cardiac transplant and that this decrease is maintained thereafter.[52] This finding reflects the rapid improvement in hemodynamic disturbances and tissue perfusion that is achieved by cardiac transplant.

Interestingly, exercise training can also substantially reduce MSNA among patients with cardiac failure; this reduction may be linked to the improved prognosis for these patients.[53-55] Four months of regular aerobic exercise training (1 hour per session 3 to 4 times per week) resulted in substantial increases in aerobic fitness, substantial increases in quality of life, and marked decreases in SNA among these patients.[54,55] It is possible that the changes in neural activity are linked to the improvements in other aspects of health that are brought about by exercise, but the mechanisms of these links remain to be determined.[54,55] This effect among patients with heart failure is particularly striking because aerobic exercise training does not generally decrease resting MSNA in healthy persons, as demonstrated by both longitudinal studies[56] and cross-sectional comparisons.[57,58]

Coronary Artery Disease

Unstable angina and acute myocardial infarction (MI) are associated with an increase in MSNA that lasts for several months.[59,60] Graham et al[60] found that MSNA was increased by 20 to 30 bursts per minute immediately after either unstable angina or acute MI. Among patients with unstable angina, MSNA returned to normal in approximately 6 months, whereas among patients with acute MI, MSNA did not return to normal until 9 months after the MI. This long-term sympathoexcitation may contribute to the elevation in cardiovascular morbidity and mortality rates after acute coronary syndromes, and further studies may show that it also has prognostic value.

Obstructive Sleep Apnea

In patients with OSA, MSNA is increased, even during the awake state without apnea.[61] Although patients with OSA are often obese, the sympathoexcitation is not attributable to obesity alone; MSNA is higher in obese persons with OSA than in those without OSA.[62] The long-term sympathoexcitation associated with OSA can be partially or completely reversed by long-term continuous positive airway pressure.[63]

The mechanisms of sympathetic activation in association with OSA include chemoreflex activation by hypoxia and hypercapnia, as well as altered baroreflex responsiveness.[64] Sympathetic activation in association with OSA, along with factors such as endothelial dysfunction, contributes to the risk of hypertension[65] and cardiovascular morbidity[64] among patients with this condition. Additionally, hypertensive patients have been shown to exhibit an exaggerated elevation in MSNA that is induced by hypoxia and hypercapnia because of increased sensitivity of the chemoreceptor responses.[45,46] Obstructive sleep apnea can be complicated by pulmonary hypertension. Primary pulmonary hypertension has been shown to be associated with increases in MSNA that are partially mediated by chemoreceptors.[66]

Dehydration

Also of relevance to the clinician are the alterations in MSNA that are seen during changes in volume status and serum osmolality. Dehydration is often associated with decreased orthostatic tolerance and an increased incidence of dizziness and syncope. As protection against excessive hypotension and its associated pathophysiology, dehydration results in sympathetic activation, including an increase in MSNA, in addition to the autonomic changes that are associated with the cause of dehydration. For example, exercise, hyperthermia, and osmolality are each associated with

autonomic effects that may be distinct from those of dehydration per se.[67] The signals that lead to an increase in sympathetic responsiveness among dehydrated persons probably include hyperosmolality, because an infusion of hypertonic saline can increase both resting MSNA and the sensitivity of the sympathetic baroreflex.[68-70] Decreases in central venous pressure are probably also important; we have noted an inverse relationship between central venous pressure and the sensitivity of the sympathetic baroreflex.[67,71]

Sympathetic activation in dehydrated persons can help maintain overall perfusion pressure. However, in the case of exercise, the associated decrease in muscle blood flow may impair performance.[72] Research in this area is relevant to our understanding of the pathophysiology of short-term dehydration among, for example, the elderly, surgical patients, or athletes, as well as in association with chronic medical conditions that are associated with decreased intravascular volume, including hypertension and heart failure.

CONCLUSION

The sympathetic nervous system plays a vital role in maintaining cardiovascular health because of its key effects on both short- and long-term regulation of blood pressure and blood flow to organs. In the past several decades, direct measurement of vasoconstrictor SNA by microneurography has provided great insight into sympathetic neural mechanisms in both health and disease. Because microneurography is both technically challenging and time-consuming, its widespread use in the clinical setting is impractical. Nonetheless, direct measurement of SNA has provided, and will continue to provide, important clinical insight into a variety of situations. Notable examples include the findings that increases in SNA may be linked to both severity and prognosis in diseases such as OSA and congestive heart failure. Interestingly, treatment (continuous positive airway pressure for OSA and heart transplant for congestive heart failure) can reverse these large increases in SNA, and this reversal may then contribute to an improved prognosis after successful treatment.

Clearly, more information is needed about SNA and its relationship to a variety of clinical conditions. With regard to the broad question of blood pressure regulation, the variability in SNA, which was originally thought to hamper our ability to gain clinical insight from MSNA, has recently been shown to provide insight into mechanisms of regulation. Recent studies that have specifically investigated this interindividual variability suggest that clinicians may ultimately be able to use it to their advantage in the new era of "individualized medicine." Increasing our understanding of integrative cardiovascular physiology, in which one mechanism that contributes to blood pressure regulation (such as vasoconstrictor SNA) may be balanced by another such mechanism (such as cardiac output), will help us to elucidate how the system works, when it works, and what may go wrong when it does not. Such knowledge will ultimately provide insight into diagnosis and treatment.

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